REMARKS

In the Office Action dated September 22, 2004, claims 1-8, 13-19, 22 and 24-31, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 1-19, 22 and 24-31 are currently pending in this application, claims 20, 21, and 23 have been canceled, claims 32-40 have been withdrawn and claims 41 and 42 added to the application.

The office action indicates that claims 9-12 are directed to a distinct invention from the originally filed claims. Claims 9-12 were previously rejected as being of improper dependent form and were rewritten to be independent claims. In this amendment claims 9-12 have been amended to clarify that the methods are for modulating the sphingolipid-cholesterol microdomain which produces the recited results. Applicants respectfully contend that claims 9-12 should be examined in the present application and request reconsideration of the withdrawal of these claims.

Claims 1-8, 13-19, 22 and 24-31 were rejected under 35 USC §112, second paragraph, as indefinite. The claims have been amended to delete or specifically define the term "derivative" and to specify the additions or substitutions on the ganglioside and cholesterol. Support for this language can be found on page 5, line 20 to page 6 line 34 and on page 7, lines 11-27 of the specification.

Claim 15 was rejected under 35 USC §103(a) as unpatentable over Ladisch. Applicants previously pointed out that Ladisch does not teach the administration of gangliosides, ganglioside derivatives and/or cholesterol derivatives in the amounts specified or the modulation of sphingolipid-cholesterol microdomains. Ladisch discloses only the addition of cholesterol (not cholesterol derivatives) to lipid emulsions to adjust a biologically normal relation of cholesterol/lecithin. Applicants point out that the administration of cholesterol would not produce the results obtained with the present invention. Cholesterol is not specific for microdomains and thus no imaginable dose would be pharmaceutically relevant to microdomain modifications. The present claims have been amended to clarify suitable cholesterol derivatives and to indicate that the administration of the cholesterol derivative is effective to increase the detergent solubility of proteins associated with sphingolipid-cholesterol domains. Applicants point out that the cholesterol derivatives in the present invention have the opposite effect as compared to Ladisch's cholesterol. In the present invention, administration of the gangliosides and cholesterol derivatives surprisingly leads to a disruption of membrane rafts. Therefore, Ladisch does not teach all the elements of claim 15, in particular:

(1) the modulation of cholesterol-lipid microdomains of a cell membrane;

(2) the administration of the claimed amounts of gangliosides and/or cholesterol sulfate, cholesterol thiosulfate, cholesterol molecules derivatized on the OH function, and cholesterol to which organic groups are added or substituted; and

(3) the administration of an amount of a cholesterol derivative which is effective to increase the detergent solubility of proteins associated with sphingolipid-cholesterol domains.

In view of the above discussion and amendments clarifying the cholesterol derivatives, applicants request that this rejection be withdrawn.

Claims 1-8, 13-19 and 24-31 were rejected under 35 USC §103(a) as unpatentable over Brown and Rietveld et al. in view of U.S. Patent No. 4,551,449 to Ladisch. As discussed above, Ladisch does not teach the modulation of cholesterol-lipid microdomains of a cell membrane, the administration of the claimed amounts of gangliosides and/or cholesterol sulfate, cholesterol thiosulfate, cholesterol molecules derivatized on the OH function, and cholesterol to which organic groups are added or substituted or the administration of an amount of a cholesterol derivative which is effective to increase the detergent solubility of proteins associated with sphingolipid-cholesterol domains. Brown does not cure this deficiency because Brown is directed to sphingolipid rafts and the interaction of other membrane lipids such as cholesterol with those rafts. Brown does not suggest or disclose cholesterol derivatives or gangliosides which increase the detergent solubility of proteins associated with sphingolipid-cholesterol domains. Rietveld was cited primarily for showing that TX-100 extraction yielded a detergent insoluble glycolipid complex (DIG) in which GPI-anchored proteins were enriched together with sphingomyelin (SM) and cholesterol and does not cure the deficiencies in Brown. Applicants point out that there is no suggestion in Rietveld that the "accumulation" of cholesterol as

discussed in Rietveld (page 472, second paragraph) is caused by adding cholesterol or cholesterol derivatives. Even if Rietveld suggested the addition of cholesterol, Rietveld indicates that it would stabilize the sphingolipid-cholesterol domains. In contrast to this, the inventors of the present invention have discovered that the opposite is true with cholesterol derivatives, gangliosides or ganglioside derivatives. That is, that the addition of cholesterol derivatives, gangliosides or ganglioside derivatives to cells increases the detergent solubility of proteins associated with such domains. This unexpected effect of external gangliosides, ganglioside derivatives and cholesterol derivatives allows one to modulate microdomains. As discussed above, the claims have been amended to clarify that the ganglioside and cholesterol derivative are in an amount effective to increase the detergent solubility of proteins associated with sphingolipid-cholesterol domains. In view of the above amendments and discussion, applicants request that this rejection be withdrawn.

Applicants respectfully submit that all of claims 1-19, 22, 24-31 and 41-42 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

By _____

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